CONGENITAL NONHEMOLYTIC JAUNDICE (CRIGLER-NAJJAR SYNDROME): REPORT OF A CASE

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CONGENITAL nonhemolytic jaundice was first reported in 1952 by Crigler and Najjar.[1] The seven infants they described formed part of a large kindred in western Maryland which was closely inbred. Six of the infants died with kernicterus in the first year of life; while the survivor, at five years of age, was reported by Childs and Najjar[2] in 1956 as being healthy despite icterus. A case of late involvement of the central nervous system was reported by Rosenthal.[3] The syndrome in a Negro child was described by Whitington[4] in 1960.

The present case is being reported because of the rarity of the condition, the absence of consanguinity, and the unusual renal findings.

Report of a Case

A four-week-old male was first examined at the Cleveland Clinic on June 15, 1962, because of persistent jaundice. His mother was gravida 2, para 2, and Rh positive. She is of Spanish descent, and has resided in the United States for six years. The father is ethnically Anglo-Saxon, and American for several generations. They stated that there was no possibility of consanguinity. The sibling, a female, aged 19 months, was in good health. The maternal grandmother was said to have been jaundiced most of her life and to have died in her eighth decade.

The mother was not a diabetic, and she received no steroids or estrogens during pregnancy. Apart from an illness described as "flu" during the second trimester, the gestation period of 36 weeks was uneventful. After the spontaneous onset of labor and an uncomplicated breech delivery, the patient was born weighing 3,005 gm. He sustained no birth trauma or respiratory difficulties, and fed well at the breast. Jaundice was first noted on the third day of life. This was attributed to "physiologic jaundice," and he was discharged from the hospital to his home on the fifth day of life. The jaundice failed to subside and he was readmitted to a local hospital, and then was transferred to the Cleveland Clinic Hospital for evaluation.‡

The physical examination revealed: a lethargic male infant, 52 cm. in length (3d percentile), weighing 3,540 gm. (3d percentile); a temperature of 37.5 C.; a pulse rate of 120; and respirations

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‡*The diagnosis of Crigler-Najjar syndrome was correctly made by the referring physician, Dr. Robert P. Ostergard, of Warren, Ohio.*

of 40 per minute. The intensely icteric skin was free of excoriations, nevi, and distended veins. There was no palpable lymphadenopathy. The size, shape, and contour of the head were normal, as was the tension of the fontanelle. The smooth, nontender, nonpulsatile edge of the liver was palpable 2 cm. below the costal margin. Splenomegaly and ascites were absent. The sclerae were icteric, but the pupillary reflexes and fundi were normal. The Moro reflex and knee jerks were active and symmetric. The feces were brown.

The laboratory findings included a blood hemoglobin concentration of 10.2 gm. per 100 ml., and a hematocrit reading of 33 percent. The red cell fragility and the reticulocyte count were normal. The blood group was A, Rh positive, and the result of the direct Coombs test was negative. The white blood cell count, differential cell count, and platelets were normal. Hepatic function studies revealed a total serum bilirubin of 29.6 mg. per 100 ml., with a direct-reacting fraction of 1 mg. per 100 ml. Other determinations were: serum transaminase, 22 SGO units; serum alkaline phosphatase, 12.5 Bodansky units; cephalin-cholesterol flocculation test, negative; and prothrombin concentration, 100 percent. The serum protein electrophoretic pattern was normal. The urine specimens contained no bile, sugar, urobilinogen, protein, or cytomegalic inclusions, but had a striking golden-yellow color. A quantitative naphthoresorcinol test for glucuronides in the urine[5] demonstrated their complete absence.

An operative cholecystocholangiogram made by Dr. Richard C. Britton,* of the Department of General Surgery, revealed evidence of a normal unobstructed biliary tree. Bile obtained from the gallbladder at the time of the operation contained 19.2 mg. of total bilirubin per 100 ml., with a direct-reacting fraction of 6.0 mg. per milliliter. A biopsy was made of the liver, and the tissue was incubated with uridine D-glucose, diphosphopyridine nucleotide, and salicylic acid at phH 7 (0.2 M. phosphate buffer) at 37 C. for eight hours.[7] A control study using normal rat liver was made at the same time. No glucuronide was formed by the specimen of the patient's liver, indicating the absence of glucuronyl transferase.

Postoperatively, signs of bilirubin encephalopathy appeared, with increasing lethargy, absence of the Moro reflex, spasms of rigidity, opisthotonos, and apneic spells. On the eighth postoperative day the patient died at the age of six and one-half weeks.

At autopsy an unusual form of kernicterus and renal papillitis were found. The hippocampus, mammillary bodies, caudate nucleus, and fornix showed the characteristic yellow staining of kernicterus. The other basal ganglia were not stained. Residual fetal lobulations were evident in the kidneys, the smooth capsules of which could be easily stripped. The renal cortex was yellow-tan, and averaged 0.2 cm. in width. The renal medulla averaged 0.4 cm. in width, and ended in yellow papillae with a golden-yellow crystalline deposit at their tips (*Fig. 1*). Sections of these areas showed focal necrosis of the collecting tubules and the intertubular parenchyma, associated with the deposition of large numbers of refractile golden-yellow crystals. These crystals were platelike, rhomboidal, or needle-shaped (*Fig. 2*), ranging in size from 1 to 6 μ. A chloroform extract of the crystal fragments gave a positive indirect Van den Bergh reaction.

The macroscopic and the histologic examinations of the liver revealed no abnormality. The bile ducts and cystic ducts were patent, and the gallbladder contained green mucilaginous bile.

A careful search for *Toxoplasma gondii* cytomegalic inclusions, or other infectious agents known to cause jaundice, was unfruitful.

Both parents had normal serum bilirubin levels, and the results of a naphthoresorcinol test of the urine specimens for glucuronide were positive.

Discussion

The conversion of indirect-reacting bilirubin to the direct-reacting or conjugated

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form is a function of the liver. Integral to the conjugating system is the enzyme, glucuronyl transferase.[7] As shown by Schmid, Hammaker, and Axelrod,[8] this

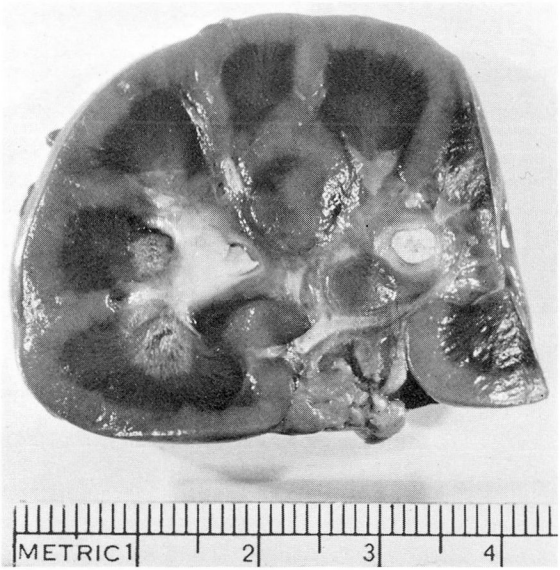

Fig. 1. Longitudinal section of the right kidney, showing bilirubin deposits at the tips of the renal papillae.

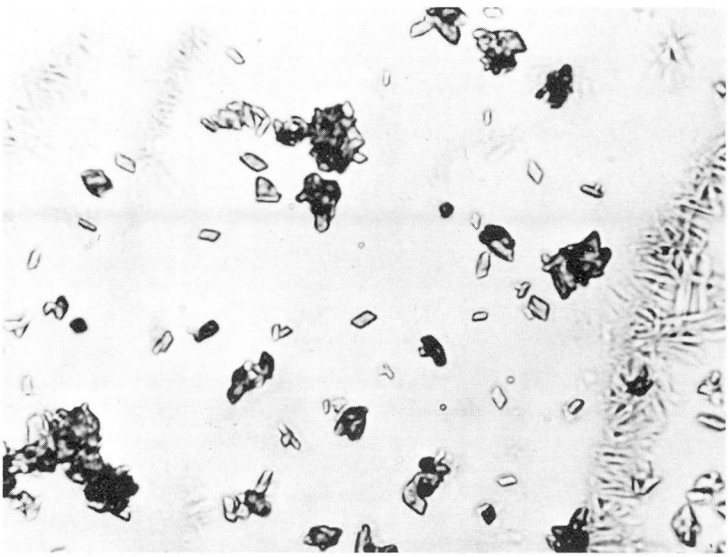

Fig. 2. Photomicrograph showing bilirubin crystals from renal papillae. Chloroform extract; magnification X 1800.

substance is located in the microsomes of hepatic parenchymal cells. It catalyzes the transfer of glucuronic acid from a specific donor (uridine diphosphate glucuronic acid) to the acceptor substance, bilirubin. Absence or deficiency of the enzyme leads to hyperbilirubinemia of the indirect type, and clinical jaundice. Lathe and Walker[9] demonstrated that such deficiency is responsible for the jaundice in homozygous Gunn rats. Genetic, chemical, and clinical features corresponding to those in Gunn rats are characteristic of the Crigler-Najjar syndrome.

Deficiency of the conjugating system is present in the neonate before the fifteenth day of life; a factor of importance in the production of so-called "physiologic jaundice."[10] Lucey, Arias, and McKay[11] have also described a transient familial neonatal hyperbilirubinemia due to a substance in maternal serum which inhibits the formation of bilirubin glucuronide. Competition for glucuronic acid by the presence of any one of a wide variety of substances, including chloramphenicol, salicylates, menthol, and steroids, may result in jaundice, but this was not a factor in our case. The infant's age at onset of symptoms, and the severity of the disease excluded Gilbert's disease.

With the onset, on the third day of life, of persistent jaundice of the acholuric nonhemolytic type that terminated in kernicterus and death, the patient closely resembled those infants described by Crigler and Najjar[1]. This view was strengthened by the high concentration of indirect-reacting bilirubin, the brown feces, the normal hepatic structure, and the complete absence of glucuronide formation.

However, in all of the cases described by Crigler and Najjar[1] there was evidence of consanguinity, while in our case there was none. Furthermore, the parents of the infant had no impairment in the formation of urinary glucuronides, in contrast to the impairment in relatives of patients with familial nonhemolytic jaundice described by Childs, Sidbury, and Migeon.[12] It seems likely, therefore, that the disease in our patient was the result of a genetic mutation. The cause of jaundice in the maternal grandmother is not known.

The finding of green bile in the gallbladder was in accord with the case described by Whitington,[4] and unlike the cases described by Schmid, Axelrod, Hammaker, and Rosenthal[13] in which there was colorless bile containing only traces of bilirubin.

The renal papillitis due to bilirubin deposition seen in this case has also been found in Gunn rats[9] and in cases of erythroblastosis.[14] It is possible that saturation of plasma-protein-binding sites by unconjugated bilirubin was followed by its transudation into the renal tubules and intertubular parenchyma where it was deposited. Since glucuronyl transferase activity in the kidney has been described by Dutton and Stevenson,[15] its local absence in our patient may also have been a factor. Though the lesions were bilateral they did not interfere with urinary output.

Summary

A case is reported of a male infant who had congenital nonhemolytic jaundice

terminating in kernicterus and his death at the age of six weeks. Jaundice began on the third day of life and was due to a high concentration of indirect-reacting bilirubin, resulting from deficiency of the enzyme glucuronyl transferase. The clinical features closely paralleled those described as the Crigler-Najjar syndrome, though consanguinity was not present. An unusual finding was bilateral renal papillitis due to bilirubin crystallization and deposition.

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